

A CLINICAL CASE OF TOURAINE-SOLENTE-GOLÉ SYNDROME

RODICA LASCU¹, DAN MIRCEA STĂNILĂ², ALINA ADRIANA PANGA³

^{1,2,3}County Clinical Emergency Hospital Sibiu

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Abstract: One of rare syndromes that can be found for one time only in one's career is this case of Pachydermoperiostosis (PDP) Touraine-Solente-Golé (TSG) syndrome. PDP or primary hypertrophic osteoarthropathy (PHO) is a rare genetic disorder that affects both the bones and the skin. The disease is also known under other terms: idiopathic hypertrophic osteoarthropathy or Touraine-Solente-Golé syndrome. It is characterized by pachydermia (skin thickening), periostosis (excessive bone formation) and tissue swelling with loss of normal angle between the nail and nail bed. This disease affects relatively more men than women. It is an inherited disorder, autosomal dominant. It begins insidiously at puberty. It is characterized by thickened skin of the face and extremities, thick and wavy scalp, primary hypertrophic osteoarthropathy. Bone and inferior soft tissue proliferation resembles to that of an elephant, hence the name of pachydermoperiostosis. After onset, the disease stabilizes after about 5 to 20 years. Lives of PDP patients can be severely damaged. Currently, the symptomatic treatment is represented by NSAIDs and steroids, or surgical procedures. In 1868, PDP was first described by Friedreich: "excessive growth of bones of the entire skeleton". Touraine, Solente and Gole described PDP as a primary form of bone disease - hypertrophic osteoarthropathy in 1935. Three forms can be distinguished.

CASE REPORT

The patient, F.V., 63 years old presented for an ophthalmologic examination for ocular discomfort due to enormous thickness of the eyelids of both eyes especially those above. The upper eyelids hang heavy as in cases of multiple chalazia.

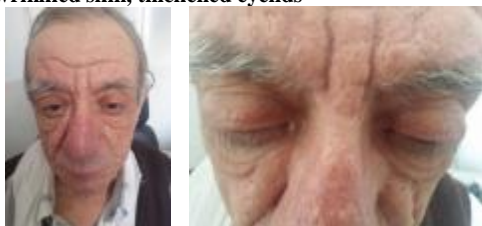
The disease has a long history. Our patient complained 10 years ago about a nodule that looks like a chalazion on the upper eyelid in both eyes. Two-three years later, these nodules began to gradually expand, so that they comprised the entire upper eyelid in both eyes.

Regarding the patient's medical family history, we learnt that his father had diabetes mellitus.

Patient's medical history: gastric ulcer operated in 1995, type II diabetes since 1980, appendectomy, fractured right forearm in 2015.

Eye examination: vision in the right eye=2/3, 1 cc; vision in the left eye=2/3, 1 cc; blood pressure in the right eye=16mmHg; blood pressure in the left eye=15mmHg; visual field in both eyes = narrowed in the upper half periphery because of the position of the eyelids.

Figure no. 1. a. and b. Face appearance. Forehead thickened and wrinkled skin, thickened eyelids



Upper lids in both eyes presented chalazia. Upon local examination, the anterior pole in both eyes looked normal. Fundus examination: myopia, myopigenic choroiditis, no changes suggestive for diabetic retinopathy.

Figure no. 2 a. and b. Hands thickened skin. Sausage-like fingers



Figure no. 3. a, b and c. Scalp skin-fold areas



¹Corresponding author: Rodica Lascu, Aleea Infanteriștilor, Bloc I, Scara B, Etaj III, Ap. 25, Sibiu, România, E-mail: lascughrodica@yahoo.com, Phone: +40720 547341

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CLINICAL ASPECTS

General investigations

Radiological examination: Radiological investigations of the skull were normal, including Sella turcica. Turkish saddle radiography: normal limits. There were no changes in the sellar floor and anatomy. Long bones of lower limbs showed minimal periosteal reaction along the shaft.

Laboratory investigations: Laboratory investigations included analysis of the growth hormone, thyroid profile and venereal diseases, Erythrocyte Sedimentation Rate (ESR), serum calcium, alkaline phosphatase.

Dermatological examination: scalp folliculitis.

Ear, nose and throat examination: Bilateral subacute submaxillitis, right retromandibular lymph nodes.

Cardiologic examination: sinus rhythm, AV 75b / min, discrete changes in the terminal phase

Pathological examination: adenomatous proliferation of Meibomius glands and cystic dilatation thereof; skin epithelium sebaceous adenomatosis and sebaceous adenomatous proliferation between the orbicularis muscle fascicles.

Based on history, clinical, laboratory and radiological findings, the patient was diagnosed with TSG syndrome.

DISCUSSIONS

Touraine-Solente-Golé (TSG) syndrome can be classified in three categories:

The complete form occurs in 40% of cases and can involve all the symptoms, but mainly pachydermia, periostosis and digital clubbing.

The incomplete form occurs in 54% of cases and is characterized by the primary effect on bones, thus occurring skeleton changes. Pachydermia is very limited.

The fruste form occurs in only 6% of cases. There are minor modifications of the skeleton, especially skin symptoms and limited periostosis.(1)

Epidemiology

Regarding *prevalence*, PDP is a rare genetic disease. There have been reported at least 204 cases of PDP. The incidence and prevalence of PDP is not yet known.(1)

In terms of distribution, PDP occurs more frequently in men than in women, with a ratio of around 7: 1. African American people are affected to a greater extent.

Hereditary: In 25-38% of cases, patients have a family history of PDP. It is suggested that the incomplete and the complete forms are inherited, either autosomal dominant (involving a dominant allele) or autosomal recessive (involving a recessive allele).(2)

Cause:

Although PDP pathogenesis is not yet fully understood, two theories have been suggested:

- Neurogenic: vagus nerve stimulation causes vasodilation, increasing blood flow and PDP.
- Humor: mediators, such as growth factors or inflammatory mediators are increased, leading to the proliferation of fibroblasts and PDP.

Role of PGE₂:

Recently, it has been suggested that PGE₂ acts as a local mediator. ProstaglandinGE₂ plays a part in the pathogenesis of PDP. In PDP patients, there were seen high levels of PGE₂ and low level of PGE-M (metabolite of PGE₂).

PGE₂ can mimic the activity of osteoblasts and osteoclasts (i.e. bone tissue building and destruction. This is why acroosteolysis and periosteal osteogenesis can be explained by the action of PGE₂. Also, PGE₂ has vasodilating effects, in accordance with local prolonged vasodilation in digital clubbing.

Elevated levels of PGE₂ in PDP patients are associated

with mutations in HPGD gene. These patients showed symptoms typical of PDP, such as digital clubbing and periostosis. HPGD gene is mapped on chromosome 4q34 encoding 15-hydroxyprostaglandin dehydrogenase enzyme (HPGD). This enzyme catalyzes the first step in the degradation of PGE₂. So far, eight different mutations are being known, which lead to a dysfunctional HPGD enzyme in PDP patients. Due to these mutations, PGE₂ substrate binding to HPGD is disturbed. As a result, PGE₂ cannot be transferred to the PGE-M and still remains in high concentrations.(3)

Numerous studies have demonstrated an important link between increased levels of prostaglandin E2 and the development of colorectal neoplasia.(4)

The role of other mediators:

In addition to elevated levels of PGE₂, studies in patients with hypertrophic osteoarthropathy have also shown increased plasma concentrations of many other mediators, such as von Willebrand factor and vascular endothelial growth factor (VEGF). These substances may also have a role in PDP progression and proliferation, in contrast to the HPGD. There have not been yet reported mutations suspected by these factors.(3)

Von Willebrand factor is a marker for platelets and endothelial activity. This suggests that the activation of endothelial cells and platelets play an important part in the pathogenesis of the PDP. VEGF promotes angiogenesis (growth of new blood vessels) and differentiation of osteoblasts, which may explain clubbing and excessive formation of fibroblasts in PDP patients. Other mediators are found in elevated concentrations in patients with PDP: osteocalcin, endothelin-1, b-thromboglobulin, growth factor, platelet-derived growth factor (PDGF) and epidermal growth factor (EGF). There has not been yet described the role of these mediators in PDP.(3)

Skin and marrow biopsy may present an exacerbated proliferation of fibroblasts, which are associated with diffuse epidermal hyperplasia and lymphocytic infiltrate with collagen redistribution. Studies have shown an increase of connective tissue, increased plasma substances, including osteocalcin, endothelin-1, β-tromboglobulin, PDGF, von Willebrand and the vascular endothelial growth factor (VEGF).(3)

In terms of *symptoms*, PDP has many visible symptoms. Clinical characteristics are most important: pachydermia (thickening and wrinkling of the skin), scalp-skin fold areas, periostosis, (periarticular tissue swelling and new bone formation in the long bones) and digital clubbing.

Digital clubbing is characterized by proliferation of soft tissue around the terminal segments of fingers and legs without bone change.

Digital clubbing is a rare inherited genetic disorder, autosomal recessive or a dominant inheritance pattern with variable penetration. It may occur as part of the syndrome of primary hypertrophic osteoarthropathy. In an isolated form, it is associated with a variety of clinical conditions: cancer, cardiovascular diseases, inflammatory disorders.(4)

Other symptoms include: excessive sweating, aches and gastrointestinal abnormalities. Eye symptoms include fallen eyelids, thick stratum corneum.

Diagnosis: The easiest way to diagnose PDP is when the following are present: pachydermia, digital clubbing and long bones periostosis. Formation of new bone under the periosteum can be detected by X-rays of long bones. Skin biopsy is another way to diagnose PDP. It is not a very specific method, as other diseases such as myxedema, hypothyroidism have the same changes. To rule out other diseases, hormonal studies are conducted.(3,5)

Prognosis: Age of onset is often at puberty. PDP

progresses, usually for 5 to 20 years, after which it stabilized. Life expectancy may be normal, with functional complications, limitation of motion and neurological symptoms.(3)

Treatment: PDP effective treatment is currently unknown. Treatment to reduce inflammation and pain include NSAIDs and corticosteroids. Treatment with botulinum toxin (BTX-A) is a simple procedure that can be used in the PDP cosmetic treatment.(6)

Surgery is used to improve the cosmetic appearance: facial lifting, wrinkles removal, surgical removal of excess facial skin, eyelid ptosis surgery.(1)

CONCLUSIONS

This case illustrates how eye manifestations of a general syndrome can betray its presence.

Clinical and radiological findings favour the current diagnosis of TSG syndrome.

Family members have been recommended clinical and radiological examinations.

The patient was referred to the department of plastic surgery to improve cosmetic appearance.

Prognosis depends largely on the degree of common implications and periarticular periosteal thickening.

Detailed investigation and early diagnosis can help preventing disability, later in life.

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